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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,913	08/06/2001	Zuomei Li	106101.145	8110

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ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/817,913	LI ET AL.	
	Examiner	Art Unit	
	ZOHREH VAKILI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-48,50,51,53 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-48,50,51,53 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 45-48, 50-51, and 53-54 are presented for examination.

Applicant's Amendment filed November 15, 2007 has been received and entered into the present application. Claims 45-48, 50-51, and 53-54 are pending and are herein examined on the merits.

Applicant's arguments, filed November 15, 2007 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Response to Arguments--Claim Rejections - 35 USC § 103

Claims 45-48, 50-51, and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwon et al. (Proc. Natl. Acad. Sci 1998. 95:3356-3361), in view of Taunton et al. (Science 1996, 272(5260)408412), Baracchini et al. (US Pat. No. 5801154), and Bennett et al. (US Pat. No. 5,998,148).

The instant obviousness rejection was set forth on the grounds that Kwon et al. teach small molecule inhibition of histone deacetylase -1 (HDAC), which can be used to reverse the morphological phenotype induced by transformation of cells with known oncogenes. Furthermore, both Bennett and Baracchini et al. teach that antisense molecules can be easily made and used to inhibit any target so long as the sequence is

known, and provide for their methods of use in humans. Therefore, one of ordinary skill in the art would have been motivated to use the sequence histone deacetylase-1 of Taunton et al. to develop antisense inhibitors for the purpose of treating neoplastic cells, because Kwon teaches that inhibition of histone deacetylase-1 can cause the reversion of oncogenically transformed cells to a normal phenotype.

In response, applicants argue that Kwon et al. is focused on the use of a small molecule inhibitor of the HDAC enzyme, and does not provide any insight into the design, targets, and desirability of antisense oligonucleotides as instantly claimed, which target HDAC gene expression.

There is agreement on this point, however, it is not considered relevant to whether or not the instantly claimed invention as obvious, since Kwon et al. was not relied upon for insight into the design, targets, and desirability of antisense oligonucleotides which target HDAC gene expression. Rather, as stated in the previous action, Bennett and Baracchini et al. are considered to teach a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene. In fact, Baracchini et al. state the following at column 4:

> Oligonucleotides have recently become accepted as drugs for the treatment of disease states in animals and man. For example, workers in the field have now identified antisense, triplex and other oligonucleotide therapeutic compositions which are capable of modulating expression of genes implicated in viral, fungal and metabolic diseases. Numerous antisense oligonucleotide drugs have been safely administered to humans and a number of clinical trials are presently underway. Efficacy has been demonstrated for several oligonucleotide drugs, directed to both viral and cellular gene targets. It is thus established that oligonucleotides can be useful therapeutics.

Both Baracchini et al. and Bennett teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Both Baracchini et al. and Bennett teach that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Both Baracchini et al and Bennett provide specific embodiments of such modifications at columns 6-8 and in Example 1. These specific examples taught by Baracchini et al include the presently claimed phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8-10. Column 4 teaches various carriers for antisense delivery. Baracchini *et al.* also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length.

Accordingly, both Baracchini et al. and Bennett are considered to be replete with all the necessary insight into the design, targeting of, and desirability of using antisense oligonucleotides against any known target, for example the instantly claimed HDAC-1 target.

Kwon et al. was relied upon to show the desirability of inhibiting the activity of HDAC-1. Kwon et al. is considered to do this, because Kwon et al. teaches inhibition of

HDAC-1 activity. As applicants are no doubt aware, inhibition of HDAC-1 activity can be accomplished by numerous routes, for example Kwon et al. explicitly teaches small molecule based inhibition of HDAC protein. As applicants are also no doubt aware, HDAC activity can also be inhibited by targeting the synthesis of the HDAC enzyme via antisense-mediated inhibition, using for example, the teachings of Bennett and et al. or Baracchini et al.

Applicants argue that Kwon actually teaches away from using anything other than natural products small molecule inhibitors of HDAC enzymes. However, these arguments are not convincing, and are, in fact, in error. Kwon et al. clearly indicates the value of inhibiting the instant HDAC-1 target, and particularly mentions the use of non-small molecule HDAC inhibitors. For example the last full paragraph on page 3361 states that "Depudecin and other HDAC inhibitors have potential value as therapeutic agents. Apicidin, a cyclic peptide related to trapoxin, has been shown to exhibit potent antiprotozoal activity by inhibition of HDAC's in parasites (36)… specific inhibition of HDAC's in endothelial cells could have therapeutic value" (emphasis added). Clearly, Kwon et al. refer to the "potential value" of "other HDAC inhibitors", including "a cyclic peptide", which is not a small molecule inhibitor.

Applicants have argued that Kwon et al. teach the pan-inhibitor of all HDAC isoforms and that Kwon et al. does not teach or suggest isotype selective histone deacetylase-1 inhibitors. This is simply in error. The only isoform used in the reference of Kwon et al. is HDAC-1. See Methods.

Taunton et al. teach the isolation and sequence of histone deacetylase-l.

Baracchini et al. teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8- 10. Column 4 teaches various carriers for antisense delivery. Baracchini et al. also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett et al. are considered to parallel those of Baracchini et al. Bennett et al. teaches general antisense targeting guidelines at columns 3-4. Bennett et al. also teaches targeting 5'-untranslated regions, start codons, coding regions, and 3'-untranslated regions of a desired target. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 6-7 teach that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate

linkages, among others. Columns 7-8 teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. Bennett et al. also teach one of ordinary skill to modify nucleobases in antisense oligonucleotides, including the teaching of 5-methylcytosine (col. 8-9), and also to use chimeric antisense oligonucleotides (col. 9-10). Bennett et al. teach that the above modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Columns 10-24 teach numerous carriers for antisense oligonucleotides. Table 1 teaches the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification). Thus, Bennett et al. is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

Finally, one would have a reasonable expectation of success given that Baracchini et al. and Bennett et al. provide a detailed blueprint for making and using modified antisense compounds targeted to a target gene, the sequence of which is provided by Taunton, and the steps of which are routine to one of ordinary skill in the art. Applicant's remarks have been fully and carefully considered in their entirety, but fail to be persuasive.

Applicant's amendments and remarks have been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

For these reasons, and those already made of record at pages 5-9 of the

previous Office Action dated July 18, 2007 of which such reasons are incorporated herein by reference, rejection of claims 45-48, 50-51, and 53-54 remain proper and is **maintained**.

Conclusion

No claims of the present application are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner 1614 June 9, 2008

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614